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EXAMINER	
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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Paper No. 21

Application Number: 08/460,186
Filing Date: June 2, 1995
Appellant(s): Von Borstel et al.

Leonard C. Mitchard
For Appellant

EXAMINER'S ANSWER

This is in response to appellant's brief on appeal filed 10-13-2000 and supplemental appeal brief filed May 15, 2001.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is correct with the exception of the 35 U.S.C. 112(1) rejection of record which is now withdrawn in view of applicant's arguments.

(7) Grouping of Claims

Appellant's brief includes a statement that claims 1-25 do not stand or fall together and provides reasons as set forth in 37 CAR 1.192(c)(7) and (c)(8).

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

The following is a listing of the prior art of record relied upon in the rejection of claims under appeal.

4,017,606 Hanze et al April 12, 1977

WO 89/03837 Von Borstel et al. May 5, 1989

Sommadossi et al. "Uridine reverses the toxicity of 3'-Azido-3'-Deoxythymidine in Normal Human Granulocyte-Macrophage Progenitor Cells in Vitro without impairment of antiretroviral activity." Antimicrobial Agents and Chemotherapy, vol. 32, no.7, pp. 997-1001. 7/1998.

Martin et al., "High Dose 5-FU with Delayed Uridine Rescue in Mice." Cancer Research, vol. 42, pp. 3964-3970. 1982.

Bhalla et al., "Deoxycytidine preferentially protects normal versus leukemic myeloid progenitor cells from cytosine arabinoside mediated cytotoxicity." Blood, vol. 70, no. 2 , pp. 568-571. 7/1987.

Falcone et al. "Differential Effectors for Benzylacylouridine on the Toxic and Therapeutic effects of Azidothymidine in Mice". Vol. 76, no. 11, pp. 2216-2221. 12/1990.

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 1-15, 18, 19, 22-25 are rejected under 35 U.S.C. 103. This rejection is set forth in prior Office action, Paper No. 5 and recited below.

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Claims 1 - 15, 18 - 19, and 22 - 25 are rejected under 35 U.S.C. § 103 as being unpatentable over Martin et al. (Cancer Res., 1982) or Sommadossi et al. (Antimicrobial Agents and Chemotherapy, 1988) view of Von Borstel et al. (WO 89/03837) and Falcone et al. (Blood, 1990).

The claims are directed to a method for treating cancer comprising administering a pyrimidine nucleoside analog and acylated uridine, deoxyuridine, cytidine or deoxycytidine.

Claims 18 and 19 include a uridine phosphorylase as an additional component.

Martin et al. teaches that administering exogenous uridine can reduce the toxicity of 5-FU and actually "rescue" mice from a toxic dose of 5-FU. Sommadossi et al. also teaches that uridine administration can reduce the toxicity of a pyrimidine nucleoside analog, AZT. Neither Martin et al. nor Sommadossi et al. teaches the use of acylated uridine or cytidine.

However, Von Borstel et al. discloses a method for elevating the serum and tissue levels of free uridine or cytidine comprising administering the acylated prodrugs thereof (see claims 10 - 15). Therefore, it would have been obvious to the person of ordinary skill in the art at the time of the invention to have substituted acylated uridine or cytidine as taught by Von Borstel et al. in place of the free uridine taught by Martin et al. and Sommadossi et al. in order to increase the serum and tissue levels of uridine and therefore, reduce the toxicity of 5-FU or AZT or any other pyrimidine nucleoside analog, regardless of the chemotherapeutic target of said nucleoside analog. Thus, the invention is prima facie obvious in the absence of clear and convincing evidence to the contrary.

Neither Martin or Sommadossi nor Von Borstel teaches the use of an inhibitor of uridine nucleoside phosphorylase as a way to increase serum and tissue levels of free uridine. However, Falcone et al. does teach the use of an inhibitor of uridine nucleoside phosphorylase, benzylacyclouridine, to increase the serum and tissue levels of free uridine, and thereby reducing the toxicity of AZT. Therefore, a method of using either acylated U or C in combination with a uridine phosphorylase inhibitor would also have been obvious to the person

or ordinary skill in the art at the time of the invention wanting to obtain the combined uridine elevating effects of two compounds known in the art to increase the bioavailability of free uridine.

Claims 16 and 17 are rejected under 35 U.S.C. 103. This rejection is set forth in prior Office action, Paper No. 5 and recited below.

Claims 16 - 17 and 20 - 21 are rejected under 35 U.S.C. § 103 as being unpatentable over Bhalla et al. (Blood, 1987) in view of Von Borstel et al. (WO 89/03838) and Hanze et al. (4,017,606).

Claims 16 - 17 are directed to a method for preventing or treating toxicity due to pyrimidine nucleoside analogs comprising the administration of a pyrimidine nucleoside analog and an acylated deoxycytidine. Claims 20 - 21 further include a cytidine deaminase inhibitor.

Bhalla et al. teaches that the administration of deoxy-cytidine reduces the toxicity of cytosine arabinoside. Bhalla does not teach the use of acylated deoxycytidine in place of free deoxycytidine. However, Von Borstel et al. does teach the use of acylated deoxycytidine in place of free deoxycytidine in order to obtain higher serum and tissue levels of deoxy-cytidine (see claim 32). Therefore, it would have been obvious to the person of ordinary skill in the art at the time of the invention to have substituted acylated deoxycytidine as taught by Von Borstel et al. for deoxycytidine as taught be Bhalla et al. for the purpose of increasing the serum and tissue levels of free deoxycytidine, thus reducing further the toxicity of cytosine arabinoside or other pyrimidine nucleoside analogs.

Neither Bhalla nor Von Borstel disclose a cytidine deaminase inhibitor. However, Hanze et al. does disclose tetrahydrouridine as a cytidine deaminase inhibitor (column 5, lines 42 - 61) and its use to prevent the degradation of a cytidine nucleoside analog. Therefore, it would have been obvious to the person of ordinary skill in the art at the time of the invention to have replaced free deoxycytidine with a combination of acylated deoxycytidine and tetrahydrouridine in order to obtain even higher levels of free cytidine in serum and tissue which would create even more reduction in the toxicity of cytidine arabinose or any other pyrimidine nucleoside analog.

The obviousness-type double patenting rejection has been placed in abeyance until allowable subject matter is indicated.

(11) Response to Argument

35 U.S.C. 103

Claims 1 - 15 and 22 - 25 claims are directed to a method for treating cancer comprising administering a pyrimidine nucleoside analog and acylated uridine, deoxyuridine, cytidine or deoxycytidine. Claims 18 and 19 include a uridine phosphorylase as an additional component.

In the supplemental appeal brief filed May 5, 2001, applicant restated that it is presumed that reliance upon Falcone is withdrawn since it is not mentioned in the June 16, 1998 Office Action in connection with the rejection under 35 U.S.C. 102 of claims 1-15, 18,

19 and 22-25. However, Falcone has never been withdrawn from the record. The office action mailed 6/16/98 stated that the rejection was maintained for the reasons already set forth on pages 2-5 of the Office action mailed 9-3-96. Although Falcone was not repeated along with Von Borstel, Martin or Sommadossi in the 6/98 office action, reference to the maintenance of the 35 U.S.C. 103 rejection which included Falcone, mailed 9-3-96, indicates that Falcone was not withdrawn; moreover the record has never reflected a statement by the examiner asserting that Falcone was withdrawn.

In the rejection of claims 18 and 19, applicant argues that the teaching of Falcone would not have motivated one to combine an inhibitor of uridine phosphorylase with a source of uridine since Falcone et al. teaches that the increased *in vivo* levels of uridine resulting from such combination did not result in reductions in AZT toxicity as compared to the uridine phosphorylase inhibitor benzylacylouridine (BAU). Claims 18 and 19 are drawn to a method for preventing or treating toxicity due to a pyrimidine nucleoside analog comprising administering to an animal a pharmaceutically effective amount of an acylated derivative of a non-methylated pyrimidine; wherein said acylated derivative of a non-methylated pyrimidine nucleoside is an acylated derivative of uridine, deoxyuridine or cytidine and includes administering an inhibitor of uridine phosphorylase, such as benzylacylouridine. However, the combination of Falcone was motivated in light of the use of acylated uridine as taught by Von Borstel to increase the plasma levels of uridine.

The elevation of plasma levels of uridine have been shown to be beneficial in both the prior art of Falcone and Von Borstel. Falcone teaches that BAU or any uridine phosphorylase inhibitor exerts it's beneficial effects by preventing the toxic degradation of uridine to uracil. Thus, the combination of two compounds, one that increases the plasma levels of uridine (which is beneficial in reducing the toxicity associated with administration of a pyrimidine nucleoside analog such as AZT), and one that prevents the toxicity associated with the degradation of plasma uridine to uracil, such as BAU or any uridine phosphorylase inhibitor, would be obvious to one of skill in the art. The citation by applicant of Falcone in the supplemental brief (paragraph bridging pp. 2219-20) only shows that exogenous nonacylated uridine does not necessarily increase the beneficial levels of plasma uridine and further supports the examiner's argument for the use of acylated uridine, as taught by Von Borstel, which does increase plasma levels of uridine.

Applicant argues that there is no motivation to combine the references. As cited in the grounds of rejection supra, the examiner recognizes that neither Martin et al. nor Sommadossi et al. teach the use of acylated uridine or cytidine. Martin et al. teaches that administering exogenous uridine can reduce the toxicity of 5-FU and actually "rescue" mice from a toxic dose of 5-FU and Sommadossi et al. also teaches that uridine administration can reduce the toxicity of a pyrimidine nucleoside analog, AZT, thus a teaching of why one of skill in the art would be motivated to acylate uridine is required as a nexus for the combination of the references. This nexus is provided by Von Borstel et al. as it discloses a method for

elevating the serum and tissue levels of free uridine or cytidine comprising administering the acylated prodrugs thereof (see claims 10 - 15). Therefore, it would have been obvious to the person of ordinary skill in the art at the time of the invention to have substituted acylated uridine (U) or cytidine (C) as taught by Von Borstel et al. in place of the free uridine taught by Martin et al. and Sommadossi et al. in order to increase the serum and tissue levels of uridine and therefore, reduce the toxicity of 5-FU or AZT or any other pyrimidine nucleoside analog, regardless of the chemotherapeutic target of said nucleoside analog. Thus, the invention is prima facie obvious in the absence of clear and convincing evidence to the contrary.

Applicants arguments are silent with respect to the motivation provided by Falcone to use an inhibitor of uridine nucleoside phosphorylase as a way to increase serum and tissue levels of free uridine. Falcone et al. does teach the use of an inhibitor of uridine nucleoside phosphorylase, benzylacylouridine, to increase the serum and tissue levels of free uridine, and thereby reducing the toxicity of AZT. Therefore, a method of using either acylated U or C in combination with a uridine phosphorylase inhibitor would also have been obvious to the person or ordinary skill in the art at the time of the invention wanting to obtain the combined uridine elevating effects of two compounds known in the art to increase the bioavailability of free uridine.

Claims 16 - 17 are directed to a method for preventing or treating toxicity due to pyrimidine nucleoside analogs comprising the administration of a pyrimidine nucleoside analog and an acylated deoxycytidine. Claims 20 - 21 further include a cytidine deaminase inhibitor.

Applicant's arguments for the combination of Bhalla et al, Von Borstel and Hanze are limited to statements that one of skill would not have been motivated to arrive at the invention; however, applicant's representative has not supported this statement with specific failures of the art nor has it been set forth specifically why the motivation set forth by the examiner is in err.

Bhalla et al. teaches that the administration of deoxy-cytidine reduces the toxicity of cytosine arabinoside. Bhalla does not teach the use of acylated deoxycytidine in place of free deoxycytidine. However, Von Borstel et al. does teach the use of acylated deoxycytidine in place of free deoxycytidine in order to obtain higher serum and tissue levels of deoxy-cytidine (see claim 32). Therefore, it would have been obvious to the person of ordinary skill in the art at the time of the invention to have substituted acylated deoxycytidine as taught by Von Borstel et al. for deoxycytidine as taught be Bhalla et al. for the purpose of increasing the serum and tissue levels of free deoxycytidine, thus reducing further the toxicity of cytosine arabinoside or other pyrimidine nucleoside analogs.

Neither Bhalla nor Von Borstel disclose a cytidine deaminase inhibitor. However, Hanze et al. does disclose tetrahydrouridine (TAU) as a cytidine deaminase inhibitor (column 5, lines 42 - 61) and its use to prevent the degradation of a cytidine nucleoside analog.

Therefore, it would have been obvious to the person of ordinary skill in the art at the time of the invention to have replaced free deoxycytidine with a combination of acylated deoxycytidine and tetrahydrouridine in order to obtain even higher levels of free cytidine in serum and tissue which would create even more reduction in the toxicity of cytidine arabinose or any other pyrimidine nucleoside analog.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

The applicant also argues against this obviousness rejection by pointing out that TAU, when coadministered with 5-FU, has unexpectedly consistently shown the ability to achieve complete regression of tumors in 60-80% of the cases. The applicant further indicates that TAU has reduced the gastrointestinal damage due to large dose of 5-FU. These unexpected results may well be sufficient to overcome the instant art rejections. However, this information is not in the specification or in affidavit form.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

HO
July 25, 2001

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Howard Owens whose telephone number is (703) 306-4538 . The examiner can normally be reached on Mon.-Fri. from 8:30 a.m. to 5 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the Primary Examiner signing this action, Gary Geist can be reached on (703) 308-1701 . The fax phone number for this Group is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-1235.

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